General

Guideline Title

Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Oct 7. 33 p. (Technology appraisal guidance; no. 357).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only:

- After the disease has progressed with ipilimumab and, for B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600 mutation-positive disease, a BRAF or mitogen-activated protein kinase (MEK) inhibitor and
- When the company provides pembrolizumab with the discount agreed in the patient access scheme

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Advanced (unresectable or metastatic) melanoma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Dermatology

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of pembrolizumab for treating advanced melanoma after disease progression with ipilimumab

Target Population

Patients with advanced melanoma (unresectable or metastatic) previously treated with ipilimumab

Interventions and Practices Considered

Pembrolizumab

Major Outcomes Considered

- Clinical effectiveness
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Tumour response rate (reported as overall response rate [ORR] and disease control rate)
  - Adverse events (AEs) of treatment
  - Health-related quality of life (HRQoL)
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG), University of Liverpool (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The company's submission (CS) adequately describes the search strategies used to identify relevant studies relating to the use of pembrolizumab for metastatic melanoma, the searches were not specific to treatment after ipilimumab or ipilimumab naïve melanoma. The company conducted two systematic searches for the clinical evidence: (1) a search for direct evidence and (2) a search for indirect evidence and adverse reactions. Full details of the strategies used to derive clinical evidence were reported in the CS (see the "Availability of Companion Documents" field). The ERG's brief description and critique of the searches is reported in Appendix 1 of the ERG report. In summary, the ERG concluded that searching was carried out to an adequate standard and accurately reflected the population and indication. The ERG is confident that the company did not miss any relevant references.

Eligibility Criteria

Appropriately, the citations identified were independently assessed for inclusion through two stages by two reviewers using the criteria shown in the table below. First, the reviewers independently scanned all abstracts and proceedings. Second, full text articles were then obtained and the same two reviewers independently reviewed these. Disagreements about whether to include a study or not were resolved by reaching consensus with the help of a third reviewer.

Table. Eligibility Criteria Used for Company's Systematic Review

Parameter	Included	Excluded
Population	Patients with unresectable stage III or IV melanoma previously treated with ipilimumab	Patients with non-cutaneous melanoma (i.e., ocular or mucosal melanoma) and with unknown primary site
Interventions	Pembrolizumab	Any other intervention
Comparators	Dacarbazine BSC*	Any other comparison
Outcomes	At least one of the following outcomes: ORR, PFS, OS	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	RCTs	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language	English	Any other language

*This intervention may be assessed in either ipilimumab-naïve or ipilimumab experienced populations.

BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

Identified Studies

Four studies were identified by the company: three randomised controlled trials (RCTs) (KEYNOTE-002, supportive KEYNOTE-001 [Part B2] and KEYNOTE-006) and the non-random KEYNOTE-001 (Part B1) study. The company states: "The second interim-analysis (IA2) of KEYNOTE-002 … provides the main evidence base for this submission." The ERG agrees that this is the only study that is directly relevant to the decision problem. The ERG provides an assessment of each study's relevance to the decision problem in Table 4 of the ERG report.

Refer to Appendix 1 of the ERG report (see the "Availability of Companion Documents" field) for additional information on search strategies for

clinical effectiveness.

Economic Evaluation

The Company's Review of Cost Effectiveness Evidence

Objective of Cost-effectiveness Review

The company undertook a search to identify studies reporting the cost effectiveness of pembrolizumab, compared with other therapies, for the treatment of patients with advanced melanoma who have progressed following treatment with ipilimumab. Details of the search strategies employed by the company are included in the CS. The databases and the initial time horizon for each search are summarised below. In all cases the searches were updated in March 2015.

Database Search Details

- Medline (via OVID SP) - 1946 to 21 July 2014
- Medline In-process (via OVID SP) - 1946 to 21 July 2014
- EMBASE - 1975 to 24 September 2014
- The Cochrane Library (including the National Health Service Economic Evaluation Database [NHS EED] and Health Technology Assessment [HTA] databases) - Searches to 17 July 2014
- Econ-Lit - 1966 to June 2014

Hand searches were also performed from several databases: the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and International Society For Pharmacoeconomics and Outcomes Research (ISPOR) conferences. These searches were constrained to the most recent 2 years (from July 2014) and updated searches were carried out in March 2015. In addition, the NICE Web site was searched to identify relevant information from previous company submissions.

Eligibility Criteria Used in the Study Selection

The company's inclusion/exclusion criteria used in the study selection are presented in the table below. The ERG is satisfied that these criteria are relevant to the decision problem.

Table. Economic Evaluation Search Inclusion/Exclusion Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Patients with advanced melanoma previously treated with ipilimumab	None
Interventions	Any medical treatment of advanced melanoma, or best supportive care, no treatment or placebo	Non-pharmacological interventions
Study type	Full economic evaluations, comparing at least two interventions in terms of cost consequence, cost minimisation, cost effectiveness, cost utility or cost benefit	Reviews (systematic or otherwise), letters and comment articles
Outcome	Studies including a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost minimisation argument	Cost-only outcomes (without a cost-minimization argument, e.g., burden of illness studies)
Publication type	Economic evaluations	Burden of illness studies
Language restrictions	Studies for which a full text version is available in English	Not available in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated. Studies that fail to present extractable results.

QALY, quality-adjusted life year

Included and Excluded Studies

No relevant studies were identified by the company.

Number of Source Documents

Clinical Effectiveness

- Only one randomised controlled trial (RCT) was of primary relevance to the decision problem.
- Three additional supportive studies (2 RCTs and one non-randomised study) were included in the review.

Cost-effectiveness

- No relevant studies were identified by the company.
- The company presented a de novo economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG), University of Liverpool (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Risk of Bias

A descriptive critical appraisal of KEYNOTE-002 and KEYNOTE-001 was conducted by the company. The company conducted the assessment using the criteria recommended by NICE for company's submissions.

Evidence Synthesis

Since only one study (KEYNOTE-002) directly compared pembrolizumab with an appropriate comparator (chemotherapy), findings were appropriately presented in a narrative. No indirect treatment comparison or mixed treatment comparison was carried out to compare pembrolizumab to other specified comparators by the company. Given patients with B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation-positive melanoma had already been pre-treated with BRAF inhibitors in the KEYNOTE-002 trial, both the company and the ERG considered that an indirect comparison of pembrolizumab with BRAF inhibitors would be inappropriate.

Since the company's literature search did not identify any studies comparing pembrolizumab to best supportive care (BSC), an indirect comparison of pembrolizumab to BSC may have been considered appropriate. However, the company's literature search did not identify any studies comparing chemotherapy to BSC in patients previously treated with ipilimumab. Therefore, the company stated it was not possible to conduct an indirect comparison in order to obtain an estimate of the efficacy of pembrolizumab relative to BSC in this patient population. The ERG concurs with the company.

The company did consider conducting a meta-analysis comparing pembrolizumab 2 kg/mg every 3 weeks (Q3W) with pembrolizumab 10 mg/kg Q3W. However from examining the progression-free survival (PFS) and overall survival (OS) outcomes in the two relevant trials (KEYNOTE-002 and KEYNOTE-001), the company concluded that the two trials were heterogeneous; the company attributed this heterogeneity to differences in the patient characteristics across the two trials (see Section 4.2 of the ERG report). Had it been possible to conduct such a meta-analysis, the results may have been informative in order to support the decision to focus on the 2 mg/kg Q3W dose of pembrolizumab. However, the ERG agrees with the company that a meta-analysis was inappropriate due to the patient populations being too dissimilar.

Refer to Section 4 of the ERG report (see the "Availability of Companion Documents" field) for additional information on clinical effectiveness analysis.

Economic Evaluation

Description of Company's Economic Model

The company has developed a de novo economic model to allow the comparison of two treatment regimens, pembrolizumab 2 mg/kg Q3W and chemotherapy/BSC. A schematic of the company's submitted economic model is provided in the company's submission (CS) and is reproduced in Figure 3 of the ERG report. It is a partitioned survival model which comprises three mutually exclusive health states: pre-progression (PFS), post-progression and death. All patients enter the model in the pre-progression state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state, i.e., patients in the pre-progression state can move to either the post-progression health state or death health state, whilst patients in the post-progression state can only move to the death health state. Estimates of OS and PFS are based on survival data from the KEYNOTE-002 clinical trial. The proportion of patients in the post-progression state is estimated as the difference between OS and PFS.

Patients receive either pembrolizumab 2 mg/kg Q3W or chemotherapy/BSC until progression. The chemotherapy/BSC arm is modelled based on chemotherapy of investigators' choice as observed in the KEYNOTE-002 clinical trial. Treatment switches to subsequent therapies are not modelled. The pre-progression and post-progression health states are associated with specific treatment, resource utilisation and adverse event (AE) costs. Time-to-death sub-states are used to capture patients' health-related quality of life (HRQoL) as a function of length of time until death (<30 days, 30 to 89 days, 90 to 179 days and ≥180 days to death).

The model has been developed in Microsoft Excel and employs a cycle length of 1 week (no half-cycle correction). The time horizon is 30 years and health effects are measured in quality-adjusted life years (QALYs). The perspective is that of the National Health Service (NHS) and cost and outcomes are discounted at an annual rate of 3.5%.

Refer to Sections 5 and 6 of the ERG report (see the "Availability of Companion Documents" field) for more information on the economic evaluation.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the Appraisal Consultation Document (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the Final Appraisal Determination (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee considered that the company's model, which compared pembrolizumab with best supportive care in people with advanced (unresectable or metastatic) melanoma after progression with ipilimumab and, for B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600 mutation-positive disease, a BRAF or mitogen-activated protein kinase (MEK) inhibitor, had a 3-state model structure that was appropriate for decision-making.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was concerned that the progression-free survival (PFS) results were immature and that it was uncertain how many and for how long people would have progression-free disease. However, it accepted that the company's approach to extrapolating PFS using a Gompertz distribution led to PFS results that appeared too optimistic because it was unlikely that people would have life-long progression-free disease.

The Committee expressed the view that the Evidence Review Group's (ERG's) approach to modelling overall survival (OS) was generally more clinically plausible than the company's model using 3 separate sources.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The company got the utility values from European Quality of Life-5 Dimensions (EQ-5D) questionnaire data from KEYNOTE-002. The utility values were incorporated into the model based on time to death.

The Committee could not identify any specific health-related benefit that had not been already captured in the quality-adjusted life year (QALY) calculation.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

None

What Are the Key Drivers of Cost-effectiveness?

The Committee understood that the variables with the biggest impact on the results were the parameters used to extrapolate PFS and the hazard ratio for OS from the 2-stage adjustment method used to extrapolate the OS results.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with best supportive care was likely to be less than £50,000 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered evidence submitted by the manufacturer of pembrolizumab and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from one randomised controlled trial (RCT). For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The evidence from KEYNOTE-002, although immature, suggested that pembrolizumab improved progression-free survival (PFS) compared with conventional chemotherapy and that, when using the 2-stage adjustment method, pembrolizumab was associated with an overall survival (OS) benefit of 3.5 months compared with chemotherapy.
- The Committee concluded that the availability of a new treatment which slows disease progression and improves quality of life when other therapies have failed is very important to patients and their families.
- Pembrolizumab is innovative because it meets a high unmet medical need and because of its low toxicity and favourable adverse effects profile compared with other treatments for metastatic melanoma.

Potential Harms

The most common (occurring in 1 in 10 people or more) adverse reactions with pembrolizumab in clinical trials were diarrhoea, nausea, itching, rash, joint pain and fatigue. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, the National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because pembrolizumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic melanoma after progression with ipilimumab and, for B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600 mutation-positive disease, a BRAF or mitogen-activated protein kinase (MEK) inhibitor, and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and Merck Sharp & Dohme have agreed that pembrolizumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Keiron Hughes (keiron.hughes@merck.com).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Oct 7. 33 p. (Technology appraisal guidance; no. 357).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Oct 7

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Dr Jane Adam (*Chair*), Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London; Professor Iain Squire (*Vice-chair*), Consultant Physician, University Hospitals of Leicester; Dr Graham Ash, Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust; Mr Adrian Griffin, Vice President, Health Technology Assessment and International Policy, Johnson & Johnson; Dr Anne McCune, Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust; Dr Mohit Misra, GP, Queen Elizabeth Hospital, London; Ms Sarah Parry, Clinical Nurse Specialist – Paediatric Pain Management, Bristol Royal Hospital for Children; Ms Pamela Rees, Lay Member; Dr Brian Shine, Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford; Dr Eldon Spackman, Research Fellow, Centre for Health Economics, University of York; Mr David Thomson, Lay member; Dr John Watkins, Clinical Senior Lecturer, Cardiff University, Consultant in Public Health Medicine, National Public Health Service Wales; Professor Olivia Wu, Professor of Health Technology Assessment, University of Glasgow; Dr Nerys Woolacott, Senior Research Fellow, Centre for Health Economics, University of York

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the National Institute for Health and Care Excellence (NICE) Web site .

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Oct. 1 p. (Technology appraisal guidance; no. 357). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Fleeman N, Bagust A, Richardson M, Krishan A, Boland A, Beale S, Stainthorpe A, Dodd S, Kotas E, Banks L, Payne M. Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab: a single technology appraisal. Liverpool (UK): Liverpool Reviews and Implementation Group (LRiG), University of Liverpool; 2015 Jul 1. 128 p. Available from the NICE Web site .
- Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab. Single technology appraisal. Manufacturer's submission. Merck Sharp & Dohme; 2015 Apr. 229 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Oct. 3 p. (Technology appraisal guidance; no. 357). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available in ePub and eBook formats

from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on December 8, 2015.

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